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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Paul K. Wolber

Serial No.: 10/699,281

Examiner: Robert Thomas Crow

Filing Date: October 30, 2003

Group Art Unit: 1634

Title: NUCLEIC ACID ARRAYS COMPRISING DEPURINATION PROBE FEATURES AND METHODS FOR USING THE SAME

COMMISSIONER FOR PATENTS
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TRANSMITTAL OF REPLY BRIEF

Sir:

Transmitted herewith is the Reply Brief with respect to the Examiner's Answer mailed on 10/11/2007 This Reply Brief is being filed pursuant to 37 CFR 1.193(b) within two months of the date of the Examiner's Answer.

(Note: Extensions of time are not allowed under 37 CFR 1.136(a))

(Note: Failure to file a Reply Brief will result in dismissal of the Appeal as to the claims made subject to an expressly stated new grounds of rejection.)

No fee is required for filing of this Reply Brief.

If any fees are required please charge Deposit Account 50-1078.

Respectfully submitted,

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By _____

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REPLY BRIEF Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	10/699,281
	Confirmation Number	3574
	Attorney Docket No.	10030355-1
	Filing Date	October 30, 2003
	First Named Inventor	WOLBER, PAUL K.
	Examiner	CROW, ROBERT
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	Title: NUCLEIC ACID ARRAYS COMPRISING DEPURINATION PROBE FEATURES AND METHODS FOR USING THE SAME	

Sir:

This Reply Brief is in response to the Examiner's Answer mailed by the Office on October 11, 2007.

Please charge any required fees to Deposit Account No. 50-1078, order number 10030355-1.

REPLY BRIEF

In this Reply Brief, the Appellants address several issues raised in the Examiner's Answer. The Appellants note that all arguments presented in the prior Appeal Brief still apply with equal force, but are not reiterated here solely in the interest of brevity and for the convenience of the Board.

With regard to the Status of Claims, the Appellants acknowledge that the rejection of Claims 21-25 under 35 U.S.C. § 102(b) as allegedly anticipated by McGall (US Patent No. 5,843,655) had been withdrawn in the Advisory Action of March 7, 2007, note that arguments made in the Appeal Brief are applicable to the rejection maintained under 35 U.S.C. § 103(a) as being unpatentable over McGall in view of Weng *et al.* (hereinafter "Weng," US Patent No. 6,691,042) and herein further reply to said rejection.

In this Reply Brief, the Appellants address specific assertions made by the Examiner in responding to Appellants' arguments. In the Examiner's Answer, the arguments are made in two general sections, the first of which, pages 3-10, reviews previous arguments for each claim and adds new arguments which are applicable to all of the claims; and the second of which, pages 10-22, contains responses to Appellants' arguments by claim group. The Examiner's assertions are therefore addressed in two sections: a first section below, which responds to the Examiner's new assertions regarding all claims, and a second section regarding the Examiner's assertions regarding the claim groups. Each section represents a separate and independent reason why the remaining rejections should be withdrawn.

I. Claims 1-13 and 21-25 are not obvious under 35 U.S.C. § 103(a) over McGall (US Patent No. 5,843,655) in view of Weng et al. (US Patent No. 6,691,042).

As discussed in the Appeal Brief, the claims are directed to a method of detecting the presence of depurination reaction products on a surface of an in situ produced nucleic acid array, the method including contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a

depurination probe with a sample including a target nucleic acid that specifically binds to the depurination probe and detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface.

The claims are rejected as allegedly being obvious over McGall in view of Weng. The Examiner acknowledges that McGall is deficient in that it fails to teach or suggest the use of a hybridization condition as a test condition for determining depurination (Final Rejection, page 5; Advisory Action, page 2). The Examiner, therefore, relies upon Weng to remedy the deficiencies of McGall. The Office asserts that it would have been obvious to modify the depurination test conditions as taught by McGall with the hybridization conditions disclosed in Weng.

In *Graham v. John Deere*, the Supreme Court set out a framework for applying the statutory language of 35 U.S.C. § 103. *Graham v. John Deere*, 383 US 1; 148 USPQ 459 (1966). This framework was reiterated in the Court's recent *KSR v. Teleflex Inc.* opinion, as follows:

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."

KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007).

The above framework may be restated as the following four factual inquires:

(A) Determining the scope and contents of the prior art;

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(B) Ascertaining the differences between the prior art and the claims in issue;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations.

With respect to framework elements A and B, courts have held that the reference or references cited in a rejection based on obviousness must teach or suggest all the elements of the claimed invention. "Subsumed within the Graham factors is a subsidiary requirement articulated by this court that where, as here, all claim limitations are found in a number of prior art references, the burden falls on the challenger of the patent to show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer v. Apotex,* 82 U.S.P.Q.2d 1321, 1330 (Fed. Cir. 2007). *See also Pharmastem Therapeutics v. Viacell et al.*, 83. U.S.P.Q. 2d 1289, 1302 (Fed. Cir. 2007) ("the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (*citing KSR Int'l Co. v. Teleflex Inc.*, 82. U.S.P.Q.2d 1385 (2007); and see *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007) ("[t]he Supreme Court recently explained that 'a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,' (*citing KSR Int'l Co.* at 1741); and see *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 80 U.S.P.Q.2d 1641, 1646 (Fed. Cir. 2006) ("[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references,' (*citing In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004))).

The requirement that the combination of references teach or suggest all elements of the claimed invention has been endorsed by the Patent & Trademark Office. According to the post-KSR Patent Office promulgated examination guidelines on determination of obviousness, when office personnel reject claims by attempting to combine prior art elements according to allegedly known methods to yield predictable results, the Office must resolve the *Graham* factual inquiries and articulate:

> (1) "a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;"
>
> (2) "a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately; and"
>
> (3) "a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable." (Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices at 57529, *citing KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (US 2007)).

Thus, the rationale to support a conclusion that a claim would have been obvious is that "all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions." *Id.* at 57529.

The Appellants argued in the Appeal Brief of June 15, 2007 that McGall describes a method for measuring depurination. In the method for measuring depurination described by McGall, oligonucleotides are synthesized *in situ* on a substrate with active sites for chemical labeling. These oligonucleotides

1) are first labeled by deprotection of the labeling site and the appropriate chemical coordination with the label, preferably a fluorophore, then

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2) exposed to conditions that cause cleavage by depurination and

3) thereafter, those labeled oligonucleotides which were not released by depurination-mediated cleavage and remain on the substrate are detected (please consult McGall, column 2, line 48 through column 3, line 6; and column 11, lines 20 to 51).

As such, McGall fails to teach any method of measuring depurination which involves hybridization. Weng is entirely silent regarding measurement of depurination events. Appellants argued that the mere teaching of hybridization by Weng does nothing to remedy the conceptual deficiencies in McGall, which explicitly teaches that chemical labeling and diminishment of label signal, which signal is present before exposure to cleavage conditions, is the way to measure depurination, and not hybridization of a depurination probe to a target nucleic acid which specifically binds to the depurination probe to detect depurination products after depurination, as is claimed.

On page 3, line 8 through the entire page 4, and similarly throughout the Examiner's Answer, the Examiner asserts that while McGall fails to teach hybridization as a test condition for depurination, Weng teaches the use of hybridization as a test condition for a nucleic acid array, thereby remedying this deficiency in McGall. The Examiner asserts that Weng provides the motivation to make this combination "because the modification would have resulted in providing a method of controlling the quality of the microarray production process as explicitly taught by Weng et al (column 5, lines 29-32)" (Examiner's Answer, page 4, line 11).

In reply, the Appellants submit that McGall, in the full knowledge of nucleic acid hybridization, nevertheless explicitly teaches that the way to measure depurination is the direct chemical labeling of oligonucleotides and quantitation of how much label remains after exposure to a depurinating condition, while Weng teaches using two-channel measurement of hybridization signals on a good quality control array vs. a test array as a means to control the quality of microarray slide production. Neither reference teaches or suggests using hybridization as a means to

test depurination. No teaching is provided in either reference which would guide the ordinarily skilled artisan to modify the primary reference so as to produce the claimed method and, indeed, the Examiner-suggested combination would require a change in the principle of operation of the primary reference such that it is no longer capable of performing its intended function.

Appellants first point out that the nature of the cited "test conditions" to which the oligonucleotides of McGall can be exposed either after labeling and before exposure to depurination conditions (McGall, column 2, line 58) or during *in situ* synthesis (McGall, column 3, line 1) is clearly defined by McGall, and does not include hybridization. The final paragraph of the section entitled "Rates of Depurination" is reproduced below for convenience:

> Various conditions used in the synthesis of a chip can be tested for the extent to which they cause depurination. For example, one method of making chips involves coating an area with a material that generates an acid upon exposure to light. Acids cause removal of acid-labile protective groups, but they also should be chosen not to cause depurination. Therefore, particular acids used in the production of chips can be tested by this method for the extent to which they cause depurination. For example, photo-acid generating ("PAG") polymer films having a photo-activatable acid, such as those used as photo-resists in the semi-conductor industry, can be applied to various areas of the substrate in order to test the effect of particular acids in the deprotection process.

As such, it is clear that the test conditions which McGall discusses with respect to depurination have no relation to hybridization of probes or nucleotides, but rather to pH and materials. McGall teaches that depurination which results from exposure to these test conditions is assessed by detection of remaining signal from the chemically modified surface-bound oligonucleotides.

The Examiner asserts that Weng fills this conceptual gap in McGall by teaching that "hybridization is used as a test condition (column 4, lines 58-67)." However, Appellants point out that the cited paragraph of Weng teaches that hybridization patterns may be corrected for fluorophore bias by combining fluor-reversed profiles. As such, the cited passage does not in fact teach using

hybridization as a test condition, but instead teaches *correcting for hybridization artifacts* by using other methods (i.e. fluor reversal, comparison of the same hybridization using different fluors).

Even assuming *arguendo* that the hybridization of Weng could reasonably be interpreted as the "test condition" of McGall, Applicants emphasize that the "test condition" of McGall is *distinct from the measurement of depurination according to McGall*. Specifically, McGall in all cases teaches the exposure of the surface-bound oligonucleotides to a "test condition", and then detecting depurination using a method which is necessarily independent of the "test condition" – specifically, the detection of remaining signal from the chemically modified surface-bound oligonucleotides. As such, the method of McGall cannot work if the test condition – which varies from assay to assay so that it can be tested (McGall, column 10, lines 21-22) – is *also the means of measuring depurination*, i.e. the hybridization of Weng.

For this reason, the Examiner-suggested combination of references does not produce the claimed invention as asserted in the Examiner's Answer at page 4, lines 12-19. In describing the results of the asserted combination, the Examiner states that the oligonucleotides of McGall are "subjected to the same *hybridization test condition* of Weng et al." (page 4, line 14). However, by collapsing "hybridization" (the asserted means of measuring depurination) and "test condition" (the experimental condition under which depurination is measured according to McGall) into a single concept in an attempt to arrive at the instant claims, the Examiner has changed the operating principle of the primary reference, specifically, from that of measuring depurination under a test condition to measuring depurination *by means of* a "test condition."

The asserted combination therefore is no longer capable of evaluating depurination under different test conditions as described by McGall. The Examiner acknowledges as much by stating that "the two ensembles of oligonucleotides in two areas of an array of McGall are both subjected to the *same* hybridization test condition of Weng et al" (Examiner's Answer, page 4, lines 13-14). If the proposed

modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti* 123 USPQ 349 (CCPA 1959). If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon* 221 USPQ 1125 (Fed. Cir. 1984).

Moreover, a mere description of "quality control" of array manufacture using "test conditions" in a secondary reference is not sufficient to teach or suggest the instant claims to the ordinarily skilled artisan in light of the teachings of McGall. There are many parameters along which the quality of array manufacture might vary, and at least as many conditions under which to test such parameters. As discussed, McGall explicitly teaches that the measurement of depurination is accomplished by chemically labeling *in situ* synthesized oligonucleotides prior to cleavage. As acknowledged by the Examiner, McGall at no point teaches or suggests hybridization with a probe as a means of testing depurination, *even while recognizing that quality control of arrays can involve testing hybridization* (McGall, column 1, lines 49-51 and column 13, lines 34-51, as cited numerous times by the Examiner). One of ordinary skill in the art would find no reason in Weng to modify the teachings of McGall in any way. The disclosure of Weng identifies no problem or issue in the disclosure of McGall which McGall does not *already address by using a method which is conceptually distinct from that of the instant claims*. Weng is entirely silent regarding depurination. Weng, in teaching dual-signal measurement of hybridization to a well-made control array to achieve quality control over test arrays, adds nothing to the disclosure of McGall and, as such, simply cannot remedy the conceptual deficiency of the primary reference without changing its operating principle, as discussed. Accordingly, the instant claims are not obvious over either reference nor their combination.

Thus, the Appellants' prior arguments still stand with equal force. The Appellants submit that all remaining rejections may be withdrawn on this basis alone.

Claim Groups I-V

The Appellants reiterate all previous arguments regarding claim groups I-V, and additionally address new elements of the Examiner's responses below.

In the Examiner's responses to arguments made regarding the claim groups, the Examiner repeatedly asserts McGall teaches hybridization of a labeled target oligonucleotide (i.e., nucleic acid) to the array and detection using a CCD imaging system (column 13, lines 33-52), and McGall specifically teaches that "the detection step involves hybridization of a labeled target oligonucleotide with an oligonucleotide in the array (column 13, lines 33-52)."

As discussed in detail in the Appeal Brief and above, the cited passage of McGall has no relevance to the detection of depurination. McGall teaches that detection of depurination is conducted by a method which does not involve hybridization but instead chemical labeling prior to exposure to cleavage conditions. The Examiner has already acknowledged this by stating that McGall does not explicitly show hybridization as a test condition for determining depurination. Appellants concur and further add that, not only is such acknowledgement not explicit, but McGall at no point teaches or suggests hybridization as a means of testing depurination, *even while recognizing that quality control of arrays can involve testing hybridization* (McGall, column 1, lines 49-51 and column 13, lines 34-51, as cited numerous times and in the present argument by the Examiner).

The Examiner also asserts on page 11 of the Examiner's Answer that Appellants agree "that the removal of depurination oligonucleotides and determination of the amount of depurination are test conditions according to McGall."

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Appellants respond that Appellants have nowhere agreed to such, and refer the Board to the cited page 9 of the Appeal Brief. Appellants state therein that "the test condition is one that is *to be evaluated for its capacity to cause depurination*, and therefore loss from the substrate, of the linkers," and further that "to the extent that McGall discloses determining the amount of depurination, it is with respect to subjecting the substrate to a test condition, *and then* determining the extent of any resultant depurination by quantitating any oligonucleotides which remain attached to the substrate" (emphases here added).

The Examiner asserts at page 13 that "examiner's interpretation of the teachings of the prior art of McGall therefore merely represents a total consideration of all of the teachings of McGall in accordance with the methodology of the ordinary artisan, wherein the sum total of the teachings of the work of another are considered as a whole." Appellants note, however, that this assertion is shown to be false by the demonstration above that the Examiner has ignored the purposes and teachings of the references in describing their combination.

As discussed in detail above, by interpreting the "test conditions" of McGall as corresponding to the hybridization of Weng in an attempt to arrive at the instant claims, the Examiner has turned McGall's conditions under which depurination is measured into the means for measuring such depurination. As such, the combination both changes the principle of operation of McGall and renders McGall inoperative for its own purposes. Such reasoning has been prohibited by the courts.

The Examiner further asserts at page 13 of the Examiner's Answer that claims 21 and 23-25 do not require hybridization as a test condition for depurination, merely requiring "detecting the presence of binding complexes of the nucleic acid ligand and the analyte on the surface of the array to detect the presence of the nucleic acid analyte in the sample," and therefore the alleged deficiency of McGall with regard to independent claim 1 is moot with regard to independent claim 21.

Appellants point out that claim 21 specifically recites "a nucleic acid ligand that specifically binds to said nucleic acid analyte with a sample suspected of comprising said analyte under conditions sufficient for binding of said analyte to said nucleic acid ligand on said array to occur," and further, "detecting the presence of binding complexes of said nucleic acid ligand and said analyte on the surface of said array." Appellants submit that the ordinarily skilled artisan is well aware that hybridization is how "binding complexes of said nucleic acid ligand and said [nucleic acid] analyte" form, and that the claimed "depurination features" and "depurination probe" function to detect depurination by hybridization, particularly in light of the specification. Accordingly, the claims are patentable because of the deficiency of McGall in this respect and the inoperability of its combination with Weng, as discussed.

In view of the foregoing discussion, the Applicants request that all remaining rejections be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: December 11, 2007

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